Updates on Cystic Fibrosis
Kimberly English MSN, RN, FNP
September 2017

History

1595- swollen hardened gleaming white pancreas (likely due to CF) from an autopsy of a “bewitched” 11 yr old girl

1848- prophecy “If it tastes salty when someone is kissed on the brow then this person is hexed [bewitched].”


1953 Dr. Paul Di Sant’ Agnese et al. Sweat Test

1955 CF foundation established

1989 Teams at University of Michigan (Dr. Frances Collins et al.) and Ontario -- Discovery of the defective CF gene on Chromosome 7

2012 Approval of Ivacaftor (Kalydeco)

2015 Approval of Ivacaftor/Lumacaftor (Orkambi)
Cystic Fibrosis

- Autosomal recessive genetic disorder
- 70,000 worldwide
  30,000 USA

Demographics

- Incidence
  - 1 in 3,300 Caucasians
  - 1 in 9,500 Hispanics
  - 1 in 15,300 African-Americans
  - 1 in 32,000 Asians
- Carrier state 1 in 25 to 30 Caucasians
- Median survival - 37 years
- Over 45% of CF patients are older than 18 years
- Newborns today expected to live into 5th or 6th decade

Newborn Screening
Genetics of Cystic Fibrosis

- Cystic fibrosis gene is on the long arm of human chromosome 7 and codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein.
- The protein is named for the disease that results from its dysfunction
- A protein at the apical epithelial surface of multiple tissues

Genetics

- Epithelial
  - Epithelia containing CFTR protein exhibit array of normal functions
    - Volume absorbing (airway, distal intestine)
    - Salt absorbing without volume (sweat ducts)
    - Volume secretory (proximal intestine, pancreas)
  - Dysfunction in CFTR gene leads to different effects on patterns of electrolyte and water transport

CFTR Dysfunction

- Increased sodium reabsorption from lumen
- Sweat glands - Inability to reabsorb chloride
  - High chloride concentration (>60 meq Cl/L) in sweat at skin surface

CFTR Dysfunction

- CF - Chloride does not get reabsorbed. Decreased chloride transport across airway lumen
- Abnormal chloride transport leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract.
Epithelial pathophysiology in cystic fibrosis, characterized by altered anion secretion, sodium hyperabsorption, and dehydration of the apical surface fluid that leads to reduced periciliary fluid volume and pH, which interferes with mucociliary clearance and innate defenses, resulting in chronic infection. The decreased periciliary fluid volume also concentrates inflammatory mediators at the immediate epithelial surface. CFTR = cystic fibrosis transmembrane conductance regulator; Cl− = chloride; ClCa = alternative chloride channel; ENaC = epithelial sodium channel; HCO3− = bicarbonate; H2O = water; Na+ = sodium.

**Figure Legend:**
- multi system disease
  - sinusitis/ nasal polyps
  - lung disease
  - pancreatic insufficiency
  - cystic fibrosis related diabetes
  - gastrointestinal dysmotility, GERD, distal intestinal obstruction syndrome (DIOS)
  - azoxepina
  - CF arthrophy/ CF arthritis
  - osteoporosis
  - liver cirrhosis, portal hypertension
  - cholelithiasis
  - urolithiasis

**CFTR Mutations (>1700)**
- Class I- Defective synthesis
- Class II- Defective processing (deF508)
- Class III- Defective regulation (G551d)
- Class IV- Defective conductance
- Class V- Reduced quantity

**Classes of CFTR Mutations.** ER = endoplasmic reticulum; mRNA = messenger RNA. See Figure 1 legend for expansion of other abbreviations.
**Treatment**

- **Major objectives**
  - Promote clearance of secretions
  - Control lung infection
  - Provide adequate nutrition
  - Prevent intestinal obstruction

- Investigation into therapies to restore the processing of misfolded CFTR protein
**Pulmonary**

- **Objectives**
  - Promote clearance of secretions
  - Control lung infection

**Chest Physiotherapy**

- **Modalities**
  - Hand percussion
  - Vibratory percussion
  - High frequency chest wall oscillation (VEST)
  - Flutter, Acapella or Therapep valves
  - Autogenic Drainage
  - Vigorous exercise

**Common Airway Pathogens**

- Sputum Culture surveillance every 3 months
  - Pseudomonas Aeruginosa
  - Staph Aureus (MSSA and MRSA)
  - Hemophilus Influenzae (non-typeable)
  - Burkholderia Cepacia
  - Stenotropomonas Maltophilia
  - Acid Fast Organisms

**Clogged pipe**
Pulmonary Medications

- Inhaled Bronchodilators
- Hypertonic Saline 7%
- Dornase Alfa (Pulmozyme)
- Inhaled Tobramycin
- Inhaled Colistin
- Inhaled Aztreonam

Targeting the Basic Defect

Gene therapy - ideal - has not worked

Failure to identify a successful viral or non-viral vector

New Therapies

- Correction of Molecular Defect
  - Ivacaftor (Kalydeco)

- Ivacaftor and Lumacaftor (Orkambi)

From: The Evolution of Cystic Fibrosis Care
Management of Cystic Fibrosis

Correcting the molecular defect in cystic fibrosis. Newer agents have mutation-specific effects on defective CFTR proteins. Class 3 or gating mutations, such as G551D, result in a defective CFTR that is unable to regulate chloride flow because of impaired ATP activation of the nucleotide-binding domains, which is corrected by the potentiator, ivacaftor. Class 2 mutations, such as delF508, result in misfolded protein that is trafficked to degradation pathways, but the corrector, lumicaftor, acts as a chaperone and traffics the defective protein to an apical surface. Nevertheless, the delF508 protein still has impaired channel function and will require addition of a potentiator to correct the chloride conductance. See Figure 1 and 2 legends for expansion of abbreviations.
Ivacaftor (Kalydeco)  
Vertex Pharmaceuticals  
- 1/31/2012  
  - 6 yrs and older  
  - G551D  
- 12/29/2014  
  - >6 yrs old  
  - Added R117H and other mutations  
- 03/18/2015  
  - 2-5 yr old  
  - Additional mutations  
- 05/17/2017  
  - Additional mutations  

**Mechanism of action:**  
- Potentiates epithelial cell chloride ion transport of defective cell-surface CFTR protein leading to improvement of the regulation of salt and water absorption and secretion in various tissues  

**Ivacaftor (Kalydeco)**  
- Decrease in sweat chloride below 60 meq Cl/L  
- Decrease in NPD (nasal potential difference)  
- Weight increase 2.5 kg  
- Improvement in symptom score  
- Improvement in FEV1  
- Pulmonary exacerbations decreased > 50%  

**Ivacaftor (Kalydeco)**  
- Children 2-<6 years  
  - <14 kg: 50 mg packet every 12 hours  
  - >14 kg: 75 mg packet every 12 hours  
- Children >6, adolescents, adults  
  - 150 mg tablet every 12 hours  
- Dosage adjustments  
  - CYP3A inhibitors and inducers  
  - Hepatic impairment
Ivacaftor (Kalydeco)

- Medication given with high fat containing food
- Avoid grapefruit and Seville oranges
- Monitor liver function tests
- Baseline and every 3 months for first year then yearly
- Side effects
- Warnings
  - Cataracts in pedi patients
  - CNS effects
  - Hepatic effects

Lumacaftor/Ivacaftor (Orkambi)

- Mechanism of action:
  - Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased procession and trafficking of mature protein to cell surface. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (gating) of the CFTR protein at the cell surface.

- Lumacaftor/Ivacaftor (Orkambi)

  - Children 6-11 year old
    - two tablets (each lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours
  - > 12 year old, adolescents, adult
    - Two tablets (each tab lumacaftor 200 mg/ivacaftor 125 mg) every 12 hours

  - Dosage adjustments
    - CYP3A inhibitors and inducers
    - Hepatic impairment

Lumacaftor/Ivacaftor (Orkambi)

- 07/02/2015
- Homozygous Delta F508
- >12 years old

- 09/28/2016
- 6-11 year old
Lumacaftor/Ivacaftor (Orkambi)

- Decrease in mean sweat chloride
- Improvement in FEV1
- Decrease in pulmonary exacerbations

Medication given with high fat containing food
- Avoid grapefruit and Seville oranges
- Monitor liver function tests
  - Baseline and every 3 months for first year then yearly
- Side effects
  - Cataracts in pedi patients
  - CNS effects
  - Hepatic effects
  - Respiratory effects

A Typical Day - Compliant Patient
Best Guideline Care

- Before work or school
  - Airway clearance
    - Nebulized bronchodilators
    - Followed by nebulized hypertonic saline
    - Followed by nebulized alfa-dornase (Pulmozyme)
    - Followed by oscillating vest (20-30 minutes). (Or Acapella device)
    - Followed by nebulized anti-pseudomonal antibiotic
    - Try to add additional midday airway clearance
    - Exercise for airway clearance
    - Repeat all above before bedtime
    - Clean your equipment daily

And there’s more

- Pancreatic enzymes with each meal and snack
- Azithromycin 3X weekly
- Water-soluble A, D, E, K vitamins twice daily with enzymes
- Proton-pump inhibitor daily or twice daily
- Ursodiol
- For many - G-tube feedings nightly
- Port flushes monthly
- AND THEN - for 70% by age 30 - Insulin-requiring DM
- CF center visits quarterly
- Hospitalization or prolonged parenteral home antibiotics - typically twice yearly
BURDEN OF CARE

- Time - Two to four hours daily
- Cost of care - $10,000 - $40,000 yearly for insured patient. Not adding new therapies. Per Month??
  - Copayments
  - Time lost from work
  - Medications and supplements not covered by insurance

Outcome Determinants

- Mutations
- Natural genotype-phenotype variation
- Socioeconomic circumstances
- Family support
- Siblings
- Insurance
- Personality factors

CF Foundation

- Access to CF Center
- www.cff.org
- https://www.cff.org/trials/pipeline